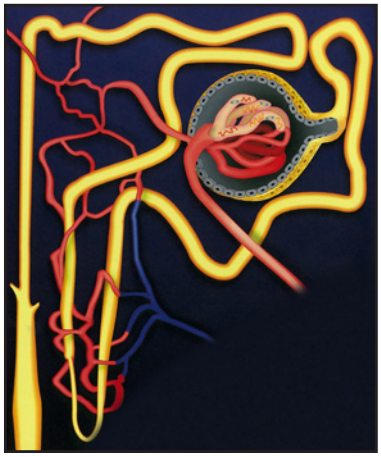
Kidney, Urologic, and Hematologic Diseases

Diseases of the kidneys, urologic system, and blood are among the most critical health problems in the U.S. They afflict millions of Americans, including children and adults. In people with chronic kidney disease, the function of these life-sustaining organs is impaired. Kidney disease may progress to irreversible kidney failure, a condition known as end-stage renal disease, in which case patients require dialysis or a kidney transplant to live. The NIDDK supports a significant portfolio of research on the biology underlying chronic kidney disease. Urologic diseases affect men, women, and children; result in significant health care expenditures; and may lead to substantial disability and impaired quality of life. The NIDDK's urology research effort includes basic, clinical, and epidemiologic research on the genitourinary tract. The NIDDK's hematology research efforts are advancing knowledge of the normal and abnormal function of blood cells and the blood-forming system. These programs seek to increase our understanding of the causes of kidney, urologic, and hematologic diseases and to enhance prevention and treatment approaches in order to lessen the burden faced by people living with these diseases.

Chronic Kidney Disease: An estimated 23 million Americans have chronic kidney disease.[3] A significant burden of chronic kidney disease is the high risk of cardiovascular disease faced by these patients. The Chronic Renal Insufficiency Cohort (CRIC) study, funded by NIDDK, aims to elucidate the relationship between chronic kidney disease and cardiovascular disease. CRIC has enrolled almost 4,000 adults with chronic kidney disease; it is the largest such study. In another NIDDK-supported effort, the African American Study of Kidney Disease and Hypertension (AASK) clinical trial, researchers assessed different interventions for kidney disease progression at over 20 academic and community medical centers throughout the country. This trial, the largest and longest study of chronic kidney disease in African Americans, found that



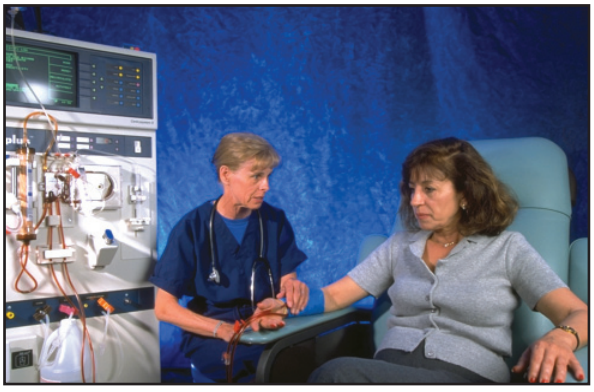
Each kidney contains about 1 million nephrons, such as the one illustrated here, which are the working units of the kidneys. Nephrons remove waste and excess fluids from the blood. *Image credit:* Maryetta Lancaster, for NIH Medical Arts and Photography Branch.

[3] *Levey AJ et al. A New Equation to Estimate Glomerular Filtration Rate.* Ann Intern Med *150: 604-612, 2009.*

an angiotensin-converting enzyme inhibitor was more effective than either a calcium channel blocker or beta-blocker in slowing kidney disease progression in African Americans with kidney disease attributed to high blood pressure. Unfortunately, this optimal treatment did not keep the disease from substantially worsening in about one-fourth of study participants. Other NIDDK-supported research suggests that interventions that target traditional risk factors—blood pressure control, blood sugar control, smoking cessation, and increased physical activity—may have the greatest potential to reduce mortality in some high-risk populations, such as the elderly.

Genetic factors likely contribute to a person's risk of developing chronic kidney disease as well. The NIDDK-supported Family Investigation of Nephropathy and Diabetes (FIND) consortium has identified four chromosomal regions that are correlated with elevated protein in the urine (a sign of impaired kidney function) or an increased risk of diabetic kidney disease.

Children and adolescents with chronic kidney disease are particularly vulnerable to its adverse effects. The CKiD study is an ongoing prospective, observational study of children with mild to moderate chronic kidney disease, taking place at over 40 medical centers. Supported by NIDDK, CKiD has enrolled several hundred children to identify the risk factors for decline in kidney function and to define how decline in kidney function impacts neurocognitive function, behavior, and other factors.



Dialysis to remove waste products and excess fluid represents a life-saving treatment for people with end-stage renal disease or kidney failure.
Photo credit: Richard Nowitz, for NIDDK.

End-stage Renal Disease: Over half a million Americans have kidney failure, also called end-stage renal disease or ESRD, and require either dialysis or a kidney transplant to live.[4] Diabetes and high blood pressure are the two leading causes of ESRD, and rates of kidney failure had been rising. After 20 years of 5 to 10 percent annual increases, however, rates of new cases of kidney failure seem to have stabilized in recent years, as reported by the U.S. Renal Data System (see sidebar). The reasons for improvement may be attributable, at least in part, to better prevention-oriented care. Unfortunately, racial disparities in ESRD rates persist, highlighting the importance of continued efforts to improve prevention and treatment approaches for kidney disease.

For patients with ESRD who are undergoing dialysis, the Dialysis Access Consortium has examined ways to improve the longevity and usefulness of two main types of vascular access sites, surgically-created sites on the body where blood is removed for cleansing and returned during dialysis. Established by the NIDDK, the Consortium is a team of researchers from universities and medical centers across the country. In one study, the anti-platelet drug clopidogrel did not improve the long-term usability of an access site called a fistula. However, in 2008, a second study by the Consortium demonstrated that a combination of aspirin and the anti-platelet drug

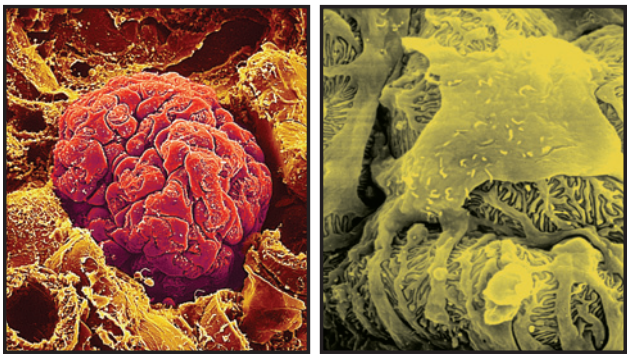
The United States Renal Data System (USRDS) is a national data system that collects, analyzes, and distributes information about end-stage renal disease (ESRD) and chronic kidney disease (CKD) in the U.S. Launched in 1988, it facilitates epidemiological and clinical research, leading to improved management of chronic kidney disease and end-stage renal disease. The USRDS is funded by the NIDDK in conjunction with the Centers for Medicare and Medicaid Services. Along with producing an Annual Data Report on CKD and ESRD in the U.S., the USRDS also publishes the Researcher's Guide, fulfills data requests, provides standard analysis files and specialized datasets to researchers, and presents the results of its research at national conferences and in peer-reviewed journals.

[4] *U.S. Renal Data System, USRDS 2009 Annual Data Report, 2009.*

dipyridamole could modestly prolong the durability of another type of access site called an AV graft.

James Willingham's kidney failure was diagnosed when he was hospitalized five years ago for an unrelated cause. James volunteered to participate in a Dialysis Access Consortium study of ways to improve access to blood vessels in patients undergoing dialysis. "It is studies like these that help people like me," James says. "The study was a very good experience."

For many years, it was unclear whether higher doses of dialysis—either prolonged dialysis or the use of high-flux filters—provided a benefit to patients. In 2002, the NIDDK-supported, multi-center HEMO Study confirmed that the minimum dialysis dose recommended by treatment guidelines is adequate and that, in general, a higher dose and special filters provide no added benefit to ESRD patients. It was the first major NIH clinical trial of dialysis in over 20 years. The ongoing Frequent Hemodialysis Network is supporting two studies comparing dialysis regimens: one will compare traditional thrice-weekly, in-center dialysis treatments with six shorter, daily treatments; a second will compare thrice weekly, in-home dialysis to six overnight treatments a week.

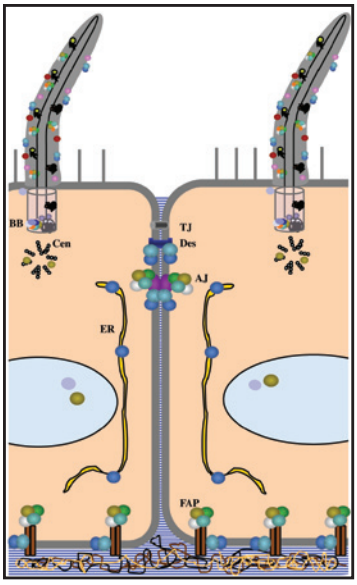


The glomerulus (left) is a small ball of capillaries that, together with surrounding cells, comprises the basic filtering unit of the kidney. The glomerulus is composed of several cell types, including podocytes (right). *Image credits:* Susumu Nishinaga/Photo Researchers, Inc. (left) and Dr. Tobias B. Huber, University Hospital Freiburg (right).

Acute Kidney Injury: Acute renal failure or acute kidney injury is a serious medical condition characterized by a relatively rapid loss of kidney function. The Veterans Affairs (VA)/NIH Acute Renal Failure Trial Network Study was conducted at 27 VA and university-affiliated medical centers, and enrolled over 1,100 critically ill patients with acute kidney injury, and compared higher-dose dialysis with less intensive, conventional dialysis. After 60 days, no significant difference in death rates was found between the two groups of patients. These results may spare patients from unnecessarily-intensive medical interventions. They also underscore the need for research into other approaches to treating acute kidney injury. Toward this end, the NIDDK has launched a study of the natural history of patients with acute kidney injury, ASSESS AKI. This study will provide important information about the natural history of acute kidney injury and recovery.

Polycystic Kidney Disease: In people with polycystic kidney disease, or PKD, fluid-filled cysts form in the kidneys and other organs and can, as they grow over time, compromise kidney function. Symptoms and complications of PKD include high blood pressure, urinary tract infections, and chronic pain. NIDDK-funded scientists have played an important role in illuminating the mechanisms underlying the two main forms of polycystic kidney disease: autosomal dominant PKD (ADPKD), the most common form, and autosomal recessive PKD (ARPKD). They found that ADPKD results from mutation of either of two genes, *PKD1* or *PKD2*, whose encoded proteins form a cell surface receptor-ion channel complex that plays a key role in kidney cell signaling and function. They also determined that ARPKD results from mutation of a single gene, *PKHD1*, which encodes a large membrane protein that localizes to the primary cilium—a tiny, hair-like projection on the cell surface. NIDDK-supported scientists have also provided important insights into the mechanisms of disease, including the discovery that cilia play an important role in sensing and cell signaling; this, in turn, sparked a new field of study into the role of cilia-mediated signaling in

other cell types. NIDDK has also supported the generation of rodent models of PKD, which have become valuable tools to study the natural history of and possible treatments for this disease. Furthermore, the identification of intracellular mediators of cell signaling has helped to identify important targets for drug development and treatment.



Proteins that are thought to play a role in polycystic kidney disease (colored spheres in this image) are involved in the assembly and function of cilia—tiny, hairlike projections on the surface of many types of cells. Research into signaling by cilia in the kidney, and its potential disruption in people with PKD, has provided new insights into possible mechanisms of disease initiation and progression and novel targets for future therapy. *Image credit*: Reprinted from *Methods in Cell Biology*, Volume 94; LF Menezes and GG Germino, Polycystic Kidney Disease, Cilia, and Planar Polarity; Copyright 2009, with permission from Elsevier.

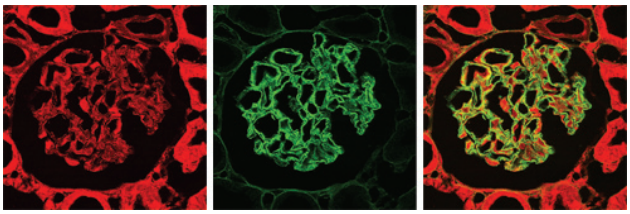
In addition to a robust portfolio of basic research projects, the NIDDK supports clinical studies aimed at furthering our knowledge about the origins, progression, and treatment of this disease. In 2006, the Consortium for Radiologic Imaging Studies of PKD (CRISP) showed that magnetic resonance imaging could accurately track structural changes in the kidneys, which may predict functional changes earlier than standard blood and urine tests in people with ADPKD. This valuable cohort of patients is being monitored through an extension of the original study. With co-funding from the PKD Foundation, the NIDDK is also supporting two clinical trials of people with ADPKD. These two trials, conducted at six sites around the country, are the largest multi-center studies of PKD conducted to date, and are collectively termed HALT-PKD. The NIDDK is also funding an interventional trial of blood pressure and cholesterol-lowering medications in children and young adults with autosomal dominant PKD to lower the risk of both heart disease and kidney failure.

In addition to these efforts, in 1999 the NIDDK established Interdisciplinary Centers for PKD Research, a partnership of scientific investigators from various disciplines who use complementary and integrated approaches in PKD research.

Focal Segmental Glomerulosclerosis: Focal segmental glomerulosclerosis (FSGS) damages the filtering units of the kidneys, thereby allowing protein and sometimes red blood cells to leak into the urine. Many patients with FSGS progress to kidney failure. Most FSGS arises from unknown causes and is termed "idiopathic" FSGS. African Americans are approximately five times more likely to develop idiopathic FSGS compared to individuals of other racial backgrounds. NIDDK intramural scientists and colleagues in the FIND consortium have found variants in the genetic region near the *MYH9* gene that seem to account for much of the increased risk for idiopathic FSGS and HIV-associated FSGS among African Americans compared to European Americans, and a portion of the increased risk for kidney disease associated with high blood pressure. Surprisingly, however, these variants were not associated with kidney failure arising from diabetes. Variation in another gene, *TRPC6*, which encodes an ion channel, is also thought to be an important

Six-year-old **Frankie Cervantes** received a kidney transplant from his mother, after his own kidneys had shut down due to the severe disease, FSGS. "I could not have been happier to learn that we matched," his mother says. The day of the transplant, Frankie was very joyful. "It's kidney day. It's kidney day," he told his parents. Because the disease could still recur, his parents are counting on medical research to help their son and others like him.

contributor to the kidney damage seen in this disease. Recent studies have found that, in some families with FSGS, the *TRPC6* gene is mutated, suggesting altered signaling by this protein may lead to kidney damage. The NIDDK is supporting a number of clinical trials aimed at improving therapy for FSGS. Many patients with FSGS do not respond to standard therapy or relapse after an initial response. The FSGS Clinical Trial is comparing two different immunosuppressive treatments for FSGS, while an NIDDK intramural trial is testing an anti-fibrotic agent in patients with FSGS. These trials seek to improve outcomes in patients with FSGS.



Kidney cells expressing the TRPC6 protein (left, red) and specialized cells called podocytes (center, green) are identified by fluorescent staining. When the images are merged (right), localization of TRPC6 to the podocytes is seen in yellow.
Image credit: Reiser J et al. Reprinted by permission from Macmillan Publishers Ltd: *Nat Genet* 37: 739-744, copyright 2005.

Urinary Tract Biology: The NIDDK supports and conducts both basic and clinical urological research. Experts have been brought together as the GenitoUrinary Development Molecular Anatomy Project (GUDMAP) consortium to assemble a molecular atlas of gene expression for the developing organs of the genitourinary tract and other tools to facilitate research.

Some children develop a condition, called vesicoureteral reflux, in which urine flows backward from the bladder to the kidney during urination. This condition is found in 30 to 50 percent of children who have had a urinary tract infection (UTI), and recurrent UTIs are thought to increase the risk of kidney damage.[5] The Randomized Intervention for Children with Vesicoureteral Reflux (RIVUR) study is designed to determine whether all children with vesicoureteral reflux should be treated with long-term antibiotics.

Andrea Arnold was diagnosed with urinary reflux when she was 6 months old, and at age 12 her damaged kidneys were removed. Andrea hopes to one day receive a kidney transplant. In the meantime, she's made friends with other patients in the dialysis center: "We don't see each other as sick. We're just close friends and we talk about everything." Researchers are striving to advance treatment for kidney disease, so that patients like Andrea and her friends will have improved health and quality of life.

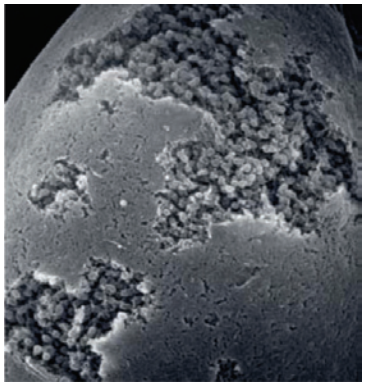
Kidney Stones—Urolithiasis and Urinary Tract Stone Disease: Kidney stone disorders are extremely painful conditions that are frequent causes of visits to health care providers. The NIDDK has a robust interest in this field, ranging from research into the basic mechanisms of stone formation and dissolution to studies of ways to improve the current minimally invasive treatment modalities of laser or ultrasound lithotripsy or extracorporal shock wave lithotripsy (ESWL) to break up stones in the body. The Institute also supports research to identify risk factors for kidney stone formation. In the 1970s and 1980s, an NIDDK-funded investigator identified many separate metabolic causes of stones, and developed several treatments. Recently, NIDDK-supported researchers made the surprising discovery that increased intake of dietary oxalate does not substantially increase risk of kidney stones, despite the fact that a large percentage of kidney stones contain a compound called calcium oxalate. Another recent study reported that the common gut bacterium, *Oxalobacter formigenes*, can break down oxalate in the digestive tract, thereby reducing the likelihood of oxalate entering the body and forming a kidney stone. Unfortunately, administration of *O. formigenes* has not been shown to

[5] *http://www.nih.gov/news/health/jun2008/niddk-20.htm*

reduce the risk of forming kidney stones, indicating that additional research into this condition is needed.

Preeclampsia: A series of research findings, from NIDDK-supported studies, may one day help women avoid a common and serious complication of pregnancy. Preeclampsia usually involves a combination of high blood pressure, swelling, impaired kidney function, and reduced blood flow to the developing fetus. Without intervention, preeclampsia can progress to a condition that is fatal for both mother and child. Placenta-derived factors are believed to be central to its development. Researchers have found increased levels of a placenta-derived protein called sFLT-1 in patients with preeclampsia. This protein can diminish the activity of two growth factors important for the maintenance and survival of blood vessels, VEGF and PlGF. Although sFLT-1 levels cannot be assessed easily for routine screening, PlGF can be measured in urine, and researchers showed that women who developed preeclampsia had abnormally low levels of PlGF several weeks earlier in their pregnancies. The ability to measure a factor in urine that may predict risk for preeclampsia represents a significant advance as a diagnostic tool. The VEGF/PlGF signaling pathway also presents multiple potential new targets for developing therapies aimed at preventing or treating this serious condition.

Research to Improve Women's Urologic Health: Many diseases of the bladder and urinary tract, such as urinary tract infections (UTIs) and urinary incontinence, are more common in women than in men. NIDDK urology research programs have spurred basic and clinical discoveries that, in turn, are leading to new or improved prevention and treatment strategies for these conditions. For example, many women suffer from recurrent UTIs, caused mostly by certain types of *Escherichia coli* (*E. coli*) bacteria. While treatable with antibiotics, the financial costs, health risks, and threat of antibiotic resistance associated with UTI therapy makes understanding these infections very important. In a discovery that could explain many recurrent UTIs, NIDDK-funded researchers have found a novel pathway by which UTI-causing *E. coli* invade, replicate in, and ultimately "hide out" in cells lining the bladder, escaping clearance by antibiotics or the immune system. Clinical



The ability of bacteria to "hide" within a pod on the surface of a mouse bladder cell may allow them to survive antibiotics, resulting in repeated, painful urinary tract infections.
Image credit: Anderson GG et al, *Science* 301: 105-107, 2003. Reprinted with permission from AAAS.

studies in women have uncovered evidence for this so-called intracellular bacterial community (IBC)-pathway in human UTIs, opening up new approaches to assessing, treating, and potentially preventing recurrent UTIs. Likewise, the results of clinical trials supported by the Institute are improving treatment options for urinary incontinence. The NIDDK-supported Urinary Incontinence Treatment Network has compared the benefits and drawbacks of two common surgeries for stress urinary incontinence in women, providing information that can help patients and providers make better informed decisions about treatment. It has also explored the potential for behavioral therapy versus drug treatment for urge incontinence. This multi-site Network is continuing its efforts with a trial to compare minimally invasive treatments for stress urinary incontinence. Independently, another NIDDK-funded clinical trial, the Program to Reduce Incontinence by Diet and Exercise (PRIDE) study, has shown that

Janet Colardo, a participant in the Program to Reduce Incontinence by Diet and Exercise (PRIDE), says she would "absolutely" recommend studies like PRIDE to others. She says that the PRIDE staff made her feel accountable to herself, as well as to them. "And I'll have the knowledge they gave me forever."

modest weight loss significantly reduces episodes of urine leakage in overweight and obese women who experience incontinence—expanding the options physicians and their patients can consider for treating incontinence in women. With NIDDK support, scientists will continue to expand on these robust findings to move urology research forward.

Chronic Urologic Pelvic Pain Syndromes: People with interstitial cystitis/painful bladder syndrome (IC/PBS) or chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) suffer from recurring discomfort or pain in the bladder and lower urinary tract and the surrounding pelvic region, as well as other symptoms. Diagnosis is difficult, and effective therapies remain elusive. Starting with the development of the first consensus research definitions for IC/PBS and CP/CPPS in the late 1980s and mid-1990s, NIDDK has sought to bolster scientific studies that could lead to better understanding, diagnosis, and prevention and treatment for these conditions. A program of basic and clinical research studies and trials has moved the field forward. Still, identifying the potential causes, risk factors, and prevalence of IC/PBS and CP/CPPS has proved challenging. These questions have been a focus of major NIDDK-supported epidemiology studies—including a study that has been conducting a cross-sectional examination of IC/PBS, prostatitis, and several other urological problems in a diverse adult population over the past several years. Another study has developed survey tools to enable researchers to identify likely cases of IC/PBS among women in the U.S. Looking to the future, NIDDK recently established the Multi-disciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network. In this Network, researchers at six "Discovery Sites" will conduct innovative, collaborative studies of IC/PBS and CP/CPPS and the potential relationships between these conditions and other chronic pain disorders, such as fibromyalgia, while scientists at two "Core Sites" will coordinate data collection, analyze tissue samples, and provide technical support. This effort capitalizes on research suggesting that clues to the cause(s) of both IC/PBS and CP/CPPS may lie outside the bladder, a promising new direction that could elucidate these challenging pain conditions.

Richard Gordon

participated in the Medical Therapy of Prostatic Symptoms clinical trial, which found a combination of two drugs to be more effective in treating the symptoms of benign prostatic hyperplasia (BPH) than either drug singly. "I'm grateful that my BPH was treated early," Richard says. "This is a problem that men should take seriously."

Advances in the Treatment of Benign Prostatic Hyperplasia: More than half of men in their sixties and as many as 90 percent in their seventies and eighties have some symptoms of benign prostatic hyperplasia (BPH), including a weak urine stream, frequent urination, and urinary tract infections. In the early 1990s, treatment of BPH generally involved a surgical procedure or one or more drug regimens. Some of these drugs acted by relaxing the smooth muscles in the prostate, allowing urine to flow more freely; others acted by inhibiting the metabolism of the male sex hormone testosterone, thereby limiting growth of the prostate. In 1994, the NIDDK launched the Medical Therapy of Prostatic Symptoms (MTOPS) trial, in which scientists at multiple medical centers compared these two kinds of drugs, used alone or together, with placebo in men with BPH. The study followed participants for an average of five years and monitored them for signs of BPH progression.

Published in 2003, the results of the MTOPS trial were unequivocal: although each drug was somewhat effective when used alone, combination therapy reduced the risk of BPH progression by 66 percent compared to placebo. The findings of the MTOPS trial validated an important nonsurgical option for BPH treatment.

HIGHLIGHTS OF NIDDK-SUPPORTED RESEARCH ADVANCES IN KIDNEY, UROLOGIC, AND HEMATOLOGIC DISEASES

1953: Researchers supported by the U.S. Public Health Service purify a kidney-derived factor, later identified as erythropoietin, that stimulates the production of red blood cells.

1960s: The discovery and characterization of the human leukocyte antigen (HLA) system sheds important light on the immune response and molecular differentiation between "self" and "non-self" cells and tissues.

1990: Urothelial uroplakins, proteins that regulate the permeability of cells lining the urinary tract, are discovered.

1990: The drug hydroxyurea is shown to relieve anemia and pain in patients with sickle cell disease. In 1998, the FDA approves it for use in adults; it remains the only such drug.

1993: Investigators localize a second gene for autosomal dominant polycystic kidney disease.

1994: The Modification of Diet in Renal Disease Study finds that a low-protein diet can slow the decline of kidney function in people with moderate kidney disease, leading to an equation to estimate kidney function.

1994: The gene for thrombopoietin, an important regulator of hematopoiesis, is cloned and characterized.

1999: Mutations in the elastase gene are found to underlie congenital neutropenia syndrome, in which very low levels of infection-fighting white blood cells leave patients vulnerable to infection.

2001: The African American Study of Kidney Disease and Hypertension (AASK) shows that angiotensin converting enzyme (ACE) inhibitors in a treatment regimen are more effective than calcium channel blockers in slowing progression of hypertensive kidney disease.

2002: The HEMO Study, the largest-ever randomized trial of hemodialysis, finds that standard dose dialysis works as well as higher doses, sparing patients unnecessary treatment.

2003: The Medical Therapy of Prostatic Symptoms (MTOPS) trial shows that combination therapy of two drugs is more effective than either drug singly in the treatment of benign prostatic hyperplasia (BPH). MTOPS is the largest and longest trial of BPH to date.

2004: Details of how hepcidin and ferroportin work to regulate the release of iron from cells are elucidated.

2005: After 20 years of annual increases of 5 to 10 percent, rates for new cases of kidney failure stabilize, according to the United States Renal Data System. Treatment strategies proven in the 1990s—such as ACE-inhibitors and angiotensin receptor blockers—and more careful control of diabetes and blood pressure, are largely credited.

2006: MRI is shown to accurately track structural changes that predict functional changes earlier than standard blood and urine tests in people with autosomal dominant PKD, according to the Consortium for Radiological Imaging Studies of PKD (CRISP).

2007: The landmark Boston Area Community Health (BACH) survey provides important data about urologic symptoms in the U.S., including prevalence and risk factors.

2008: The Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network, which will conduct highly collaborative research of the most common urologic chronic pelvic pain syndromes from a broadened systemic perspective, is launched.

2008: The VA/NIH Acute Renal Failure Trial Network (ATN) Study finds that standard dose dialysis works as well as higher doses in patients with acute kidney failure.

2008: Researchers describe genetic variations in the *MYH9* gene, which is thought to contribute to non-diabetic end-stage renal disease in African Americans.

2009: The NIDDK-supported Program to Reduce Incontinence by Diet and Exercise (PRIDE) study finds that modest weight loss results in a reduction of weekly urinary incontinence episodes by nearly one-half in overweight and obese women.

2009: The M-type phospholipase A2 receptor (PLA_2R) is implicated in up to 70 percent of cases of the kidney disease idiopathic membranous nephropathy.

2009: Researchers report success with a modified blood stem-cell transplant regimen to treat adult patients with sickle cell disease.

Hematology Research: The NIDDK's multi-faceted hematology research program focuses on understanding basic cellular and molecular mechanisms that underlie the production and function of blood cells in health and disease, and NIDDK-supported scientists have played an important role in many seminal breakthroughs over the years. NIDDK-funded research in the 1950s and 1960s contributed to the discovery of the human leukocyte antigen (HLA) system, cell-surface proteins that help the immune system differentiate between "self" and "non-self" cells. These findings facilitated improved success rates for organ transplantation, as HLA typing allowed physicians to minimize the risk of rejection. Variations in HLA types are also thought to play a role in the susceptibility of certain individuals to autoimmune diseases such as lupus, rheumatoid arthritis, and type 1 diabetes.

Beginning with research in the 1970s, the molecular and genetic bases of many congenital blood disorders have been elucidated by NIDDK-supported researchers. Advances have included the application of molecular genetic techniques to facilitate diagnosis of hemoglobin disorders such as thalassemia and sickle cell disease. NIDDK researchers contributed to the discovery, purification, and characterization of key hormones that regulate blood cell production, including the purification of erythropoietin in 1977, which led to the subsequent cloning of the gene for this hormone—which controls the production of red blood cells—in 1985, and the gene for thrombopoietin—which regulates the production of platelets by the bone marrow—in 1994. In the late 1990s, NIDDK-supported scientists identified the genetic basis of congenital neutropenias, a family of hereditary disorders characterized by an abnormally low number of an important type of white blood cell that leaves patients susceptible to infection.

Iron is a critical component of hemoglobin, and total body iron must be carefully balanced, as iron overload can damage organs and is potentially fatal, while iron deficiency impairs red blood cell production and causes anemia. Over the past decade, research supported by the NIDDK has led to important insights into how iron levels are maintained within an acceptable range, and how dysregulation of regulatory proteins (such as hepcidin, hemojuvelin, and ferroportin) can lead to too

much or too little available iron for the support of red blood cell production.

EDUCATION PROGRAMS

The NIDDK's National Kidney Disease Education Program (NKDEP) was established to raise awareness of the seriousness of kidney disease, the importance of testing those at high risk—those with diabetes, high blood pressure, cardiovascular disease, or a family history of kidney disease—and the availability of treatment to prevent or slow kidney failure. Kidney disease often has no symptoms, but if detected early, it can be treated. Current education efforts for the public include campaigns aimed at individuals with diabetes or high blood pressure, African Americans, and Hispanic audiences, with materials available in both English and Spanish; additional campaigns target health care providers and laboratory professionals (www.nkdep.nih.gov). The NIDDK also supports the National Kidney and Urologic Diseases Information Clearinghouse, which was established in 1987 to increase knowledge and understanding about diseases of the kidneys and urologic system among people with these conditions and their families, health care professionals, and the general public. An awareness campaign has helped to improve public and healthcare provider knowledge about interstitial cystitis/painful bladder syndrome (IC/PBS). The NIDDK's National Hematologic Diseases Information Service provides information and publications and responds to public inquiries.

Information from the National Kidney Disease Education Program.

LOOKING TO THE FUTURE

Photo credit: Getty Images.

Moving forward, the NIDDK is hopeful that its research portfolio will continue to provide scientific insights and improvements in patient care. As always, an important component of the Institute's support for biomedical research is its strategic planning. Often, initiatives and funding solicitations emerge from opportunities identified through this planning process, which reflect both broad scientific review and input from key stakeholders. Planning may occur in an *ad hoc* process, or may be organized under the auspices of the Kidney, Urologic, and Hematologic Diseases Interagency Coordinating Committee, and sometimes involves partnering with professional and/or patient advocacy groups. Examples of recent plans include a *Research Progress Report and Strategic Plan for Pediatric Urology*, released in 2006, and a *Prostate Research Strategic Plan*, released in 2008. Through these efforts, the NIDDK seeks to steer the research enterprise in a way that follows science while maximizing the return on the Institute's investment in order to improve the lives of patients and their families.